



(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
06.07.2005 Bulletin 2005/27

(51) Int Cl.7: **A61K 9/107**, A61K 47/10,
A61K 31/55, A61K 31/435,
A61K 31/445

(21) Application number: **01117396.0**

(22) Date of filing: **26.10.1995**

(54) **Pharmaceutical compositions**

Arzneimittel

Compositions pharmaceutiques

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE**

(30) Priority: **26.10.1994 GB 9421612**
04.11.1994 GB 9422306
22.02.1995 GB 9503553

(43) Date of publication of application:
24.10.2001 Bulletin 2001/43

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
95936554.5 / 0 786 986

(73) Proprietors:
• **Novartis AG**
4056 Basel (CH)
Designated Contracting States:
BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
• **Novartis Pharma GmbH**
1230 Wien (AT)
Designated Contracting States:
AT

(72) Inventors:
• **Jackman, Martin**
4055 Basel (CH)
• **Popp, Xue-Ping**
4125 Riehen (CH)

• **Richter, Friedrich**
67157 Wachenheim/Weinstrasse (DE)
• **Schmook, Fritz**
1130 Vienna (AT)

(74) Representative: **de Weerd, Petrus G.W. et al**
Novartis International AG
Corporate Intellectual Property
4002 Basel (CH)

(56) References cited:
EP-A- 0 423 714 **EP-A- 0 474 126**
EP-A- 0 483 842 **DE-A- 4 418 115**

• **DATABASE CHEMABS [Online] CHEMICAL
ABSTRACTS SERVICE, COLUMBUS, OHIO, US;**
**KAGAYAMA, AKIRA ET AL: "Pharmaceutical
emulsions of tricyclic compound
immunosuppressants" retrieved from STN
Database accession no. 122:142531 CA
XP002176317 & JP 06 183970 A (FUJISAWA
PHARMACEUTICAL CO., JAPAN) 5 July 1994
(1994-07-05)**

Remarks:

The file contains technical information submitted
after the application was filed and not included in this
specification

Description

[0001] The present invention relates to topical pharmaceutical compositions comprising a macrolide, and in particular to formulations which comprise a macrolide such as an ascromycin, a rapamycin or a compound of the FK506 class.

[0002] FK506 is a known macrolide antibiotic that is produced by *Streptomyces tsukubaensis* No 9993. It is also a potent immunosuppressant. The structure of FK506 is given in the appendix to the Merck Index, 11th Edition as item A5. Methods of preparing FK506 are described in EP 184162.

[0003] A large number of derivatives, antagonists, agonists and analogues of FK506, which retain the basic structure and at least one of the biological properties (for example immunological properties) of FK506, are now known. These compounds are described in a large number of publications, for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385, WO 93/5059 and the like. These compounds are termed collectively compounds of the FK506 class.

[0004] It is also known (for example from EP 315978 and EP 474126) that compounds of the FK506 class are extremely useful in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses.

[0005] Ointments containing a compound of the FK506 class and solubilizing and adsorption promoting agents to dissolve the compound are disclosed in EP 474126. Various organic solvents are proposed as solubilizing and adsorption promoting agents. However the compositions disclosed in EP 474126 are oil based compositions and do not contain water.

[0006] Compositions that contain water have been reported in the literature and FK506 compounds have also been formulated as fine suspensions (EP 484936).

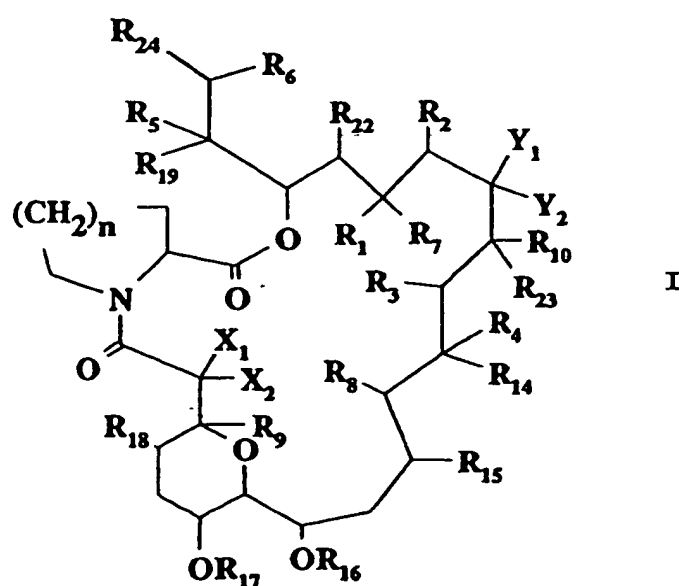
[0007] Emulsions for oral or intravenous administration containing a compound of the FK506 class have been reported in the literature in EP 483 842 and JP 61 83 970.

[0008] It has now been surprisingly found that compounds of the FK506 class can be formulated into stable emulsions. Emulsions, since they contain an aqueous phase, are much less occlusive than oil-based compositions and hence are better tolerated in many situations.

[0009] Accordingly, in one aspect, this invention provides a topical composition, in the form of an emulsion, that comprises a compound of the FK506 class; a physiologically acceptable alkanediol, ether diol or diether alcohol containing up to 8 carbon atoms as solvent for the compound of the FK506 class; and water, characterized in that it further comprises an unsaturated fatty alcohol.

[0010] This topical composition is effective, well tolerated on the skin, and reasonably to extremely stable.

[0011] In this specification, "a compound of the FK506 class" is a compound which has the same basic structure as FK506 and which has at least one of the biological properties of FK506 (for example immunosuppressant properties). The compound may be in free base form or pharmaceutically acceptable, acid addition, salt form. Examples of compounds of the FK506 class are compounds of the formula I



in which:

each adjacent pair of R_1 and R_2 , R_3 and R_4 , and R_5 and R_6 independently (a) is a pair of H atoms but R_2 may also be alkyl or (b) forms a second bond between the carbon atoms to which they are attached;

R_7 is H, OH, a protected OH group, a formyloxy group or an alkoxy group, or R_7 together with R_1 forms an oxo group; R_8 and R_9 are independently H or OH;

R_{10} is H, an alkyl group, an alkyl group substituted by one or more OH groups, an alkenyl group, an alkenyl group substituted by one or more OH groups, or an alkyl group substituted by an oxo group;

X_1 is H or OH;

X_2 is H; or

X_1 and X_2 together are an oxo group or $-\text{CH}_2\text{O}-$;

Y_1 is H or OH;

Y_2 is H; or

Y_1 and Y_2 together are an oxo group, $\text{N-NR}_{11}\text{R}_{12}$ or N-OR_{13} ;

R_{11} and R_{12} independently are H, an alkyl group, an aryl group or a tosyl group;

R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{22} , and R_{23} are independently H, or an alkyl group;

R_{24} is an optionally substituted ring system which may contain one or more heteroatoms;

n is 1, 2 or 3;

or Y_1 , Y_2 , R_{10} and R_{23} , together with the carbon atoms to which they are attached, are a saturated or unsaturated 5- or 6-membered nitrogen, sulphur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from alkyl, OH, alkoxy, benzyl, $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$ and alkyl substituted by one or more OH groups; in free base or in acid addition form.

[0012] Preferably R_{24} is selected from (a) a 3,4-di-oxo-cyclohexyl group, (b) a 3- R_{20} -4- R_{21} -cyclohexyl group in which R_{20} is OH, an alkoxy group, or a $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ group, and R_{21} is OH, $-\text{OCN}$, an alkoxy group, a $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ group, a protected hydroxy group, chloro, bromo, iodo, methylthiomethoxy, isobutanoyloxy, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy or $R_{25}R_{26}\text{CHCOO}-$ in which R_{25} is optionally protected hydroxy or optionally protected amino and R_{26} is H or methyl, or R_{20} and R_{21} together form an oxygen atom in an epoxide ring, or (c) a 5- or 6-membered cycloalkyl group which may be optionally substituted. For example R_{24} may be a cyclopentyl group substituted by methoxymethyl, optionally protected hydroxymethyl, acyloxymethyl (in which the acyl moiety optionally contains either a dimethylamino group which may be quaternized, or a carboxy group which may be esterified), or one or more amino and/or hydroxy groups which may be protected, or aminooxalyloxymethyl. A preferred example is a 2-formyl-cyclopentyl group.

[0013] Suitable alkyl groups, alkenyl groups, aryl groups, protecting groups and acyl groups are defined in EP 484936.

[0014] The macrolide used in the compositions of the present invention preferably has immunosuppressant properties. The macrolide may be rapamycin or an O-substituted derivative in which the hydroxy in position 40 of formula A illustrated at page 1 of WO 95/16691, incorporated herein by reference, is replaced by $-\text{OR}_1$ in which R_1 is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting Rapamycin (or dihydro or deoxorapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as $\text{CCl}_3\text{C}(\text{NH})\text{O}$ or CF_3SO_3) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is $\text{CCl}_3\text{C}(\text{NH})\text{O}$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3 .

[0015] A preferred compound is 40-O-(2-hydroxy)ethyl rapamycin (hereinafter compound A) as disclosed in WO 94/09010.

[0016] A preferred compound of the FK 506 class is disclosed in EP 427 680, e.g. Example 66a (also called 33-epi-chloro-33-desoxyascomycin) hereinafter compound B. Other preferred compounds of the FK 506 class are disclosed in EP 465 426, EP 569 337, and in EP 626 385, for example the compound of Example 6d in EP 569 337 hereinafter compound C, or the compound of Example 8 of EP 626385 hereinafter compound D.

[0017] Examples of alkanediol solvents which are capable of dissolving compounds of the FK506 class are propylene glycol (1,2-propanediol), butylene glycol, 2-ethyl-1,3-hexanediol, hexylene glycol (2-methyl-2,4-pentanediol) and the like. Examples of ether diol solvents are dipropylene glycol, diethyleneglycol and the like. Examples of diether alcohol solvents are diethyleneglycol mono ethyl ether and the like. Preferably the solvent is hexylene glycol. The solvent is preferably present in an amount of about 5 to about 50% w/w, more preferably 5 to 20% w/w and even more preferably

5 to 10% w/w of the emulsion.

[0018] The oil phase of the emulsion may comprise about 20 to about 80% w/w, more preferably 25 to 75 % and even more preferably 35 to 65 % by weight of the composition. The emulsion may be an oil in water emulsion or a water in oil emulsion. The oil in water emulsion may be in the form of an emulsion gel (in which case the continuous aqueous phase may be thickened using a polymeric thickener), or in the form of a cream.

[0019] The unsaturated fatty alcohol forms part of the oil phase of the emulsion and is preferably a lanolin alcohol or a C₁₆ to C₁₈ fatty alcohol; more preferably oleyl alcohol, or elaidic alcohol, although oleyl alcohol is particularly preferred. The composition preferably contains sufficient amounts of the unsaturated fatty alcohol to promote absorption of the compound of the FK506 class in the skin, more preferably about 2 to about 10 % w/w and even more preferably 5 to 10% w/w.

[0020] The oil phase also may contain other liquid oils, thickening agents and fatty bases usually used in topical compositions.

[0021] Suitable liquid oils include medium chain triglycerides obtained from fractionated vegetable oils, such as capryl/caprinic acid triglycerides. One example of such a triglyceride is commercially available under the trade name Miglyol 812 (which has a molecular weight of about 520, a n_D^{20} of about 1.448 to 1.450 and a viscosity of 0.28 to 0.32 Pa·s). The liquid oil may comprise about 5 to about 60% w/w of the emulsion and preferably 5 to 15 % w/w.

[0022] Suitable thickening agents include conventional stiffeners such as cetyl alcohol, cetostearyl alcohol, stearyl alcohol, hydrogenated castor oil (Cutina HR), Yellow wax, White wax, cetyl ester wax, emulsifying wax, microcrystalline wax, and the like. Preferably the thickening agent forms about 2 to about 30% w/w of the emulsion and more preferably 2 to 10% w/w.

[0023] Suitable fatty bases include bases such as natural wax, Vaseline (petroleum jelly, also available commercially as Petrolatum), thick paraffin, wool wax alcohols (such as those sold under the trade marks Eucerinum or Eucerin), wool wax derivatives, triglyceride waxes (such as that available under the trade name Softisan 378) and the like.

[0024] The composition may also include suitable emulsifiers as is usual in emulsion compositions. Such emulsifiers are described in standard texts such as Fiedler, H. P.; 1989; Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor, D-7960 Aulendorf, Germany and Handbook of Pharmaceutical Excipients, A Joint Publication of the American Pharmaceutical Association, Washington DC, USA and the Pharmaceutical Society of Great Britain, London, UK; 1986. Examples of suitable emulsifiers include:

(a) propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate (which is commercially available under the trade mark Miglyol 840), propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, and propylene glycol stearate;

(b) polyoxyethylene sorbitan fatty acid esters, such as mono- and tri-lauryl, palmityl, stearyl and oleyl esters. Examples of commercially available esters are those available under the trade name Tween (see Fiedler, pages 1300 to 1304) and particularly Tween 60 (polyoxyethylene(20) sorbitan mono stearate) and Tween 80 (polyoxyethylene (20) sorbitan mono oleate);

(c) polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj (See Fiedler, pages 834 and 835) and in particular Myrj 52 (which has a D^{25} of about 1.1, a melting point of about 40 to 44 °C, and a HLB value of about 16.9);

(d) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers such as those known and commercially available under the trade names Pluronic, Emkalyx and Poloxamer (see Fiedler, page 959) and in particular Pluronic F68 (which has a melting point of about 52°C and a molecular weight of about 6800 to 8975) and Poloxamer 188;

(e) dioctylsulfosuccinate or di-[2-ethylhexyl]-succinate;

(f) phospholipids and in particular lecithins (see Fiedler, pages 943 and 944);

(g) salts of fatty alcohol sulphates such as sodium lauryl sulfate and sodium cetyl stearyl sulphate;

(h) sorbitan fatty acid esters such as sorbitan mono stearate and sorbitan mono oleate which are commercially available under the trade marks Arlacel 60 (which has an HLB of about 4.7 and a melting point of about 53°C) and Span 80 (which has a D^{25} of about 1, an HLB of about 4.3 and a viscosity of about 950 to 1100 cP); (i) glycerine mono stearate which is available under the trade name Imwitor (see Fiedler, page 645) and particularly Imwitor 960;

(j) esters of polyethylene-glycol glycerol ethers, that have at least one free hydroxyl group, and aliphatic C₆-C₂₂ carboxylic acids. Examples include PEG-20 glycerine mono stearate;

(k) reaction products of a natural or hydrogenated castor oil and ethylene oxide and of which examples are available under the trade name Cremophor such as Cremophor RH 40 (having a saponification no. of about 50 to 60, an acid number of <1, an n_D^{60} of about 1.453 to 1.457 and an HLB value of about 14 to 16), Cremophor RH 60 (having a saponification no. of about 40 to 50, an acid number of <1, an n_D^{25} of about 1.453 to 1.457 and an HLB value of about 15 to 17) and Cremophor EL (having a saponification no. of about 65 to 70, an acid number of about 2, an n_D^{25} of about 1.471 and a molecular weight of about 1630). Also suitable are various tensides available under the trade names Nikkol, Emulgin, Mapeg and Incrocas (see Fiedler);

- (l) stearic acid;
 (m) oil and wax based emulsifiers such as cetyl alcohol and emulsifying wax;
 (n) polyoxyethylene glycerides such as those available under the trade name Labrafil M2130 CS (See Fiedler, page 707);
 5 (o) polyoxyethylene alkyl ethers such as polyoxyethylene stearyl ether, polyoxyethylene oleyl ether and polyoxyethylene cetyl ether which are available under the Brij and Cetomacrogol series trade names (see Fiedler, pages 222 to 224 and 284);
 (p) glycerine sorbitan fatty acid esters such as that available under the trade name Arlacel 481 (which has a molecular weight of about 630 and an HLB value of about 4.5) and
 10 (q) mixtures thereof.

[0025] Preferably the emulsifier is selected from polyethyleneglycol (20) glycerine monostearate, sorbitan mono stearate (Arlacel 60), sorbitan mono oleate (Span 60), Tween 60, Tween 80, glycerine mono stearate (Imwitor 960), stearic acid, cetyl alcohol, wool wax derivatives and alcohols and Labrafil M2130 CS and mixtures thereof. If the emulsion is a water in oil emulsion, the emulsifier selected preferably has a HLB value of 10 to 15. If the emulsion is an oil in water emulsion, the emulsifier selected preferably has a HLB value of 4 to 8. Preferably the emulsifiers are present in an amount of about 1 to about 30 % w/w and preferably 10 to 25 % w/w.

[0026] Gelling agents may also be added to provide a gelled emulsion. Suitable gelling agents are carbomers (polyacrylic acid derivatives); such as those available under the trade name Carbopol (see Fiedler, pages 254 to 256) . Carbopol 974 and Carbopol 1342 are preferred. The gelling agents are preferably present in an amount of 0.2 to 2% w/w; more preferably less than about 1% w/w.

[0027] The emulsion may also include preserving agents and anti-oxidants such as benzyl alcohol, butyl-hydroxytoluene, ascorbyl palmitate, sodium pyrosulphite, butyl hydroxy anisole, propyl p-hydroxybenzoate (available commercially, for example, under the trade name Paraben), methyl p-hydroxybenzoate (available commercially, e.g. as Paraben), sorbic acid and tocopherol. The preserving agents and anti-oxidants serve to prevent bacterial growth, and are preferably present in an amount of about 0.01 to about 2.5 % w/w. pH modifying agents may be included to bring the pH of the emulsion to between 4 and 6 or by adding a pharmaceutically acceptable buffer system. A pH of between 4 and 6 is desirable to avoid skin irritation.

[0028] The aqueous phase of the emulsion may comprise about 20 to about 80 % w/w, more preferably 25 to 75 % and even more preferably 35 to 65 % of the emulsion. The aqueous phase is preferably in the form of sterilized water.

[0029] The compound of the FK506 class is preferably present in the emulsion in an amount of about 0.01 to about 10% w/w and more preferably in an amount of 0.1 to 1 % w/w.

[0030] Preferably the compound of the FK506 class and the unsaturated fatty alcohol are present in a weight ratio of 1:1000 to 5:1; preferably 1:100 to 1:5.

[0031] It has now been surprisingly found that macrolides can be formulated into stable pharmaceutical compositions, when the compounds are in suspensions.

[0032] Accordingly, in another aspect, this invention provides a topical pharmaceutical composition that comprises a macrolide in suspension.

[0033] The term macrolide has the meaning as described above.

[0034] The pharmaceutical composition may be in solid form, but preferably it is in semi solid form suitable for topical administration.

[0035] This suspension compositions of this invention are effective, well tolerated on skin, and reasonably to extremely stable.

[0036] The suspension contains particles of macrolide of from about 5, e.g from 10, to about 90 microns in diameter. The particles of the macrolide may be produced in conventional manner, e.g. by grinding or milling.

[0037] The suspension may be prepared as a cream, a water-free ointment, a water-in-oil emulsion, an oil-in-water emulsion, an emulsion gel or a gel.

[0038] In another aspect, this invention provides a topical composition in the form of an oil-in-water emulsion gel comprising

- 50 a) a macrolide in an amount of up to 5 weight %,
 b) a thickener in an amount of up to 20 weight %,
 c) a hydrophilic component in an amount of up to 40 weight %,
 d) one or more organic acids in a total amount of up to 5 weight %
 55 e) one or more stabilisers in a total amount of up to 5 weight %,
 f) water in an amount of up to 90% by weight.

[0039] Suitable thickeners are as defined above and may include paraffin, waxes, and petrolatum.

[0040] Appropriate hydrophilic components include propylene glycol, alcohols such as cetyl alcohol, stearyl alcohol and oleyl alcohol.

[0041] Examples of suitable organic acids contemplated for use in this invention include sorbic acid. The acid functions as a preservative and serves to substantially prevent bacterial growth.

[0042] In another aspect the invention provides a topical composition in the form of an emulsion or suspension as defined above for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

[0043] In another aspect the invention provides a method of treating inflammatory or hyperproliferative skin diseases or of cutaneous manifestations of immunologically-mediated diseases comprising administering a topical composition as defined above to the skin of a patient in need thereof.

[0044] In yet another aspect, the invention provides the use of a compound of the FK506 class; a physiologically acceptable alkanediol, ether diol or diether alcohol containing up to 8 carbon atoms as solvent for the compound of the FK506 class; an unsaturated fatty alcohol and water in the preparation of a medicament in the form of an emulsion for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

[0045] The emulsion compositions may be obtained by dissolving the compound of the FK506 class in the solvent and the unsaturated fatty alcohol to provide the oil phase. If desired liquid oils, fatty bases and thickening agents may be mixed into the oil phase. The oil phase is then emulsified with the aqueous phase and, if necessary, suitable emulsifiers. Other excipients may be added at the appropriate time to the appropriate phase as is conventional.

[0046] The present applicants have found that macrolides may be unstable in topical compositions. It is believed that this instability is caused by degradation or rearrangement pathways which are not completely understood. After extensive experimental work, the applicants have found that an unsaturated fatty alcohol may be used to stabilise macrolide compositions.

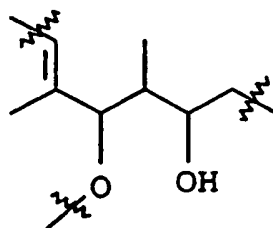
[0047] In a further aspect, this invention provides the use of an unsaturated fatty alcohol in stabilising a macrolide in a pharmaceutical composition.

[0048] In another aspect, this invention provides a method of stabilising a macrolide in a pharmaceutical composition, which method comprises mixing an unsaturated fatty alcohol with the macrolide.

[0049] The unsaturated fatty alcohol may be a C₈-C₂₂ alcohol, or may comprise a mixture of alcohols. The unsaturated fatty alcohol may have one, two or three double bonds. Preferably the unsaturated fatty alcohol has one double bond, and a cis configuration. Oleyl alcohol is preferred. A stabilising effect may be observed at a weight ratio of unsaturated fatty alcohol to active agent of at least about 1:5, for example 1:2 to 1:1 or greater, e.g. about 5:1.

[0050] The present applicants have found that the unsaturated fatty alcohol, e.g. oleyl alcohol, is suitable for stabilising a macrolide in a topical pharmaceutical composition. Examples of topical compositions are as described herein.

[0051] The unsaturated fatty alcohol, e.g. oleyl alcohol, may be used to stabilise a macrolide having at least one moiety as follows:



[0052] The present applicants have found that oleyl alcohol is useful in stabilising ascomycins and compounds of the FK 506 class, for example FK 506, ascomycin and 33-epi-chloro-33-desoxyascomycin.

[0053] The topical compositions defined above are useful in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases. Examples of such diseases are psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and Alopecia areata.

[0054] The utility of the topical compositions can be observed in standard clinical tests such as the test set out in Example 12 *infra* using a concentration of 0.01 to 10 % w/w (preferably 0.1 to 1 % w/w) of the compound of the FK506 class. The utility can also be observed using standard animals models as described in EP 315978.

[0055] The exact amount of the compound of the FK506 class and of the composition to be administered depends

EP 1 147 766 B1

on several factors, for example the desired duration of treatment and the rate of release of the compound of the FK506 class. Satisfactory results are obtained in larger mammals, for example humans, with the local application over the area to be treated of a 0.01 to 10 % w/w, preferably 0.1 to 3%, concentration of the compound of the FK506 class once or several times a day (for example 2 to 5 times a day). In general the composition may be applied to areas of skin as small as 1 cm² to as large as 1 m². Suitable skin loadings of the compound of the FK506 class fall within the range of 0.1 mg/cm² to 1 mg/cm².

[0056] The compositions of this invention are well tolerated on skin. Good skin penetration and permeation rates may be achieved using the compositions of this invention.

[0057] The compositions described in Examples 13, 14 and 19 *infra* are preferred emulsion compositions for application to mammals, e.g. humans.

[0058] For the compounds

(i) [3S-[3R*[E(1S*,3S*,4S*)],4S*,-5R*,8S*,9E,2R*,14R*,15S*,16R*,18S*,-19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl]]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,

(ii) [3S-[3R*[E(1S*,3S*,4S*)],4S*,-5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,-19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl]]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, and

(iii) [3S-(3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,-17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-(3-hydroxymethylcyclopentyl)-1-methylethenyl]]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, topical application of concentrations of 0.01 to 1 % w/w once a day is effective in the treatment of chronic plaque psoriasis in humans. In these applications the compositions are as effective as the ultra-potent Clobetasol composition (0.05%).

[0059] The following Examples describe compositions of this invention.

[0060] In the Examples,

"compound 1" is the compound [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl]]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. This compound is better known as FK506.

"Compound 2" is the compound [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,-14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-(3-hydroxymethylcyclopentyl)-1-methylethenyl]]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. This compound and a method of producing it are described in EP 465426.

"Compound 3" is [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,-19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl]]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. This compound is known as ascomycin.

[0061] Compound A, compound B, compound C and compound D have the respective meanings as described above.

[0062] The term stable, as used in the following Examples, will be understood to mean that no separation of components is observed of the respective composition when stored at room temperature for a period of four months or longer.

[0063] Chemical analysis of the active agent is undertaken using reverse phase HPLC with UV detection; $\lambda = 210$ nm. Quantification limit is 0.1% by weight.

[0064] Tolerability of the compositions is carried out, *in vivo*, on pig skin and on human skin. A visual assessment is made at 0.5, 1, 2 and 4 hours after application.

EP 1 147 766 B1

Example 1

[0065] An oil in water emulsion is prepared containing the following ingredients (in parts by weight):

5

Compound 2	0.10
Oleyl alcohol	10.00
Miglyol 812	10.00
Hexylene glycol	10.00
Cetyl alcohol	5.00
Stearyl alcohol	5.00
Benzyl alcohol	1.00
Sorbitan mono stearate	2.00
Tween 80	4.00
Glycerine mono stearate	3.00
Water	49.90

10

15

[0066] The composition is prepared by mixing together the compound 2, the oleyl alcohol, the Miglyol 812, the hexylene glycol, the cetyl alcohol and the stearyl alcohol and heating to 65°C until all components are dissolved. The Arlacel 60, Tween 80 (polyoxyethylene(20)sorbitanmonooleate) and glycerine mono stearate are then added to the oil phase and stirred until all components are dissolved. The water is then heated in a vessel containing a stirrer and homogenizer. The benzyl alcohol is then added. The oil phase is then slowly added while stirring and homogenizing until a homogenous emulsion with a droplet size of less than 20 µm is obtained. The emulsion is then cooled to room temperature. The emulsion is stable.

20

25

Example 2

[0067] An oil in water emulsion is prepared in a manner analogous to that in Example 1, and containing the following ingredients (in parts by weight):

30

Compound 1	0.10
Oleyl alcohol	10.00
Miglyol 812	10.00
Hexylene glycol	10.00
Cetyl alcohol	5.00
Stearyl alcohol	5.00
Benzyl alcohol	1.00
Sorbitan mono stearate	2.00
Tween 80	4.00
Glycerine mono stearate	3.00
Water	49.90

35

40

[0068] The emulsion is stable. No component separation is observed.

45

Example 3

[0069] A water in oil emulsion is prepared in a manner analogous to that in Example 1 except that the water is added slowly to the oil phase. The composition contains the following ingredients (in parts by weight):

50

Compound 2	0.10
Oleyl alcohol	5.00
Hexylene glycol	5.00
Yellow wax	3.00
Benzyl alcohol	1.00
Arlacel 481	7.00

55

EP 1 147 766 B1

(continued)

5

White Petroleum	15.00
Thick Paraffin	5.00
Water	58.4
MgSO ₄ ·7H ₂ O	0.5

[0070] The emulsion is stable.

10

Example 4

[0071] An oil in water emulsion is prepared in a manner analogous to that in Example 1, and containing the following ingredients (in parts by weight):

15

Compound 2	0.10
Oleyl alcohol	7.50
PEG-glycerine monostearate	7.00
propylene glycol	10.00
Cetyl alcohol	6.00
Glycerine mono stearate	4.00
Paraffin (thick)	10.00
White Petroleum	15.50
Sorbic acid	0.01
Water	39.89

20

25

Examples 5, 6 and 7

30

[0072] Oil in water emulsions are prepared in a manner analogous to that in Example 1, and containing the following ingredients (in parts by weight):

Example	5	6	7
Compound 2	1.00		
Compound 1		0.10	1.00
Oleyl alcohol	7.50	7.50	7.50
PEG-glycerine monostearate	7.00	7.00	7.00
propylene glycol	10.00	10.00	10.00
Cetyl alcohol	6.00	6.00	6.00
Glycerine mono stearate	4.00	4.00	4.00
Paraffin (thick)	10.00	10.00	10.00
White Petroleum	15.50	15.50	15.50
Sorbic acid	0.01	0.01	0.01
Water	38.99	39.89	38.99

35

40

45

Examples 8 to 11

50

[0073] The following emulsions are prepared in an analogous manner to that in Example 1.

Example	8	9	10	11
Compound 3	0.10	0.10	0.10	0.10
Hexylene glycol	5.00	10.00	10.00	5.00
Cetyl palmitate	2.00	-	-	-
Oleyl alcohol	-	10.00	10.00	-
Lanolin alcohols	-	-	-	1.50

55

EP 1 147 766 B1

(continued)

Example	8	9	10	11
MC* triglycerides	-	10.00	10.00	5.00
Isopropyl myristate	8.00	-	-	-
Cetyl alcohol	4.00	5.00	5.00	2.00
Stearyl alcohol	4.00	5.00	-	2.00
Benzyl alcohol	1.00	1.00	1.00	1.00
Sorbitan monostearate	1.90	2.00	-	3.00
Sorbitan monooleate	-	4.00	-	-
Glycerin monostearate	-	3.00	10.00	-
Tween 80	6.10	-	-	-
Petroleum, white	-	-	-	23.50
Water	67.90	49.90	53.90	56.40
Magnesium sulfate, heptahydrate	-	-	-	0.50

* MC = medium chain, e.g. Miglyol 812.

[0074] The compositions of Examples 4 to 11 are stable.

Example 12

[0075] A single centre, double-blind, placebo-controlled trial is conducted to determine the efficacy of the compositions of Examples 4 to 7 in chronic plaque psoriasis. 10 patients who are over 18 years of age, have chronic plaque psoriasis and who have not had systemic or topical therapy for chronic plaque psoriasis, within 1 month and 1 week respectively, are chosen. On day -1, scales are removed with a topical composition containing 10 % salicylic acid in Vaseline. On day 0, the compositions of examples 4 to 7, a 0.05% Clobetasol composition available under the trade mark Dermovate and a placebo are applied to the desquamated plaques under semi-occlusive conditions and left for 24 hours.

[0076] The patient is allowed to bath and the lesions are dried gently. The lesions are evaluated visually (erythema) and by palpation (infiltration) with scores ranging from 0 (absent) to 3 (severe). The procedure is repeated daily until the 10/11 day.

[0077] The cumulative scores are presented in tables 1 and 2.

Table 1:

Erythema Scores							
day	0	2	4	6	8	10	11
Example 3	30	20.5	15	11.5	9	6	7.5
Example 4	30	21.5	17.0	12	9.5	6	6.5
Example 5	30	22	17	11	8	5.5	5
Example 6	30	20	15.5	10	8.5	4.5	4.5
Placebo	30	28	25.5	25	23	23	22.5
Dermovate	30	20	13.5	10.5	8.5	8.0	8.0

Table 2:

Infiltration Scores							
day	0	2	4	6	8	10	11
Example 3	30	21	15.5	12	5.5	2	3
Example 4	30	24	16.5	12	6.5	3	2.5
Example 5	30	21.5	17	12	5	2	2
Example 6	30	21.5	14.5	10	5.5	2.5	1.5
Placebo	30	28.5	24.5	23	21	19	18.5

EP 1 147 766 B1

Table 2: (continued)

Infiltration Scores							
day	0	2	4	6	8	10	11
Dermovate	30	19	14	8	3.5	2	2.5

[0078] No adverse events are observed with the compositions of examples 4 to 7 but skin atrophy is observed in 2 patients receiving Dermovate. However the compositions of examples 4 to 7 are at least as effective as Dermovate.

[0079] The active agent used in the compositions described in Examples 1 to 11 may be replaced by Compound A, B, C or D.

Examples 13 to 16

[0080] Oil in water emulsions are prepared in analogous manner to Example 1 and having the following compositions.

Example	13	14	15	16
Oleyl alcohol	10	10	10	10
Miglyol 812	15	15	15	15
Cetyl alcohol	4	4		
Stearyl alcohol	4	4		
Glycerol monostearate	2	2		
Sorbitan monostearate	3			
Polysorbate 20			5	
Polysorbate 60	5			
Sodium cetylstearyl sulphate		1		
Methyl Paraben	0.07	0.07	0.07	0.07
Propyl Paraben	0.03	0.03	0.03	0.03
Carbopol 974p			1	0.3
Carbopol 1382				0.7
Compound B	0.3	0.3	0.3	0.3
Citrate buffer pH 5.5	0.05	0.05		
Propylene glycol	5	5	10	10
aqueous NaOH 5% wt/vol			2.5	2.5
Water	to 100	to 100	to 100	to 100

[0081] The compositions of Examples 13 to 16 are well-tolerated on pig skin and on human skin. Assay of main degradation product is 0.1% (quantification limit) for compositions 15 and 16 after 72 hours at 70°C; the oleyl alcohol is replaced by Miglyol 812 and assay of main degradation product increases to 0.5%. No separation of components is observed when stored at room temperature for four months.

Examples 17 to 19

[0082] Oil in water emulsion compositions are prepared having 1 wt-% active agent.

Example	17	18	19
Oleyl alcohol	2.5	5	10
Miglyol 812	22.5	20	15

EP 1 147 766 B1

(continued)

Example	17	18	19
Cetyl alcohol	4	4	4
Stearyl alcohol	4	4	4
Glycerol monostearate	2	2	2
Sorbitan monostearate	3	3	3
Polysorbate 60	5	5	5
Methyl Paraben	0.07	0.07	0.07
Propyl Paraben	0.03	0.03	0.03
Citric acid	0.05	0.05	0.05
NaOH 1M abs. wt./100g	0.02	0.02	0.02
Propylene glycol	5	5	5
Compound B	1	1	1
Demin. water	to 100	to 100	to 100

[0083] The emulsions of Examples 17, 18 and 19 are stable and no separation of components is observed. The compositions are found to be well-tolerated on human skin. The compositions are stored at 40°C for eight weeks and chemical analysis undertaken using HPLC. Assay of main degradation product for compositions 17, 18 and 19 is 1.1%, 0.8% and 0.4% respectively.

[0084] In the compositions of Examples 13 to 19, the active agent compound B may be replaced by compound A, compound C, compound D, compound 1, compound 2 or compound 3.

Example 20

[0085] An oil in water emulsion composition is prepared as a cream using compound C as active agent:

Component	Amount weight-%
Compound C	0.3
hexylene glycol	10
oleyl alcohol	10
Miglyol 812	10
methyl Paraben	0.07
propyl Paraben	0.03
cetylalcohol	5
glycerol monostearate	10
water	to 100

[0086] The cream is stable and no separation of components is observed.

Examples 21 to 30

[0087] Suspension compositions are prepared in Examples 21 to 30.

Example 21

[0088] A topical suspension composition is prepared containing the following ingredients (in parts by weight):

Compound 1, 2, 3, A, B, C or D	0.10
Petroleum jelly	99.9

EP 1 147 766 B1

[0089] The composition is prepared by mixing together the compound and other excipients.

Example 22

5 **[0090]** A single centre, double-blind, placebo-controlled trial is conducted to determine the efficacy of the compositions of Example 21 in chronic plaque psoriasis. 10 patients who are over 18 years of age, have chronic plaque psoriasis and who have not had systemic or topical therapy for chronic plaque psoriasis, within 1 month and 1 week respectively, are chosen. On day 1, scales are removed with a topical composition containing 10 % salicylic acid in Vaseline. On day 0, the compositions of Example 21, a 0.05% Clobetasol composition available under the trade mark Dermovate and a placebo are applied to the desquamated plaques under semi-occlusive conditions and left for 24 hours.

10 **[0091]** The patient is allowed to bath and the lesions are dried gently. The lesions are evaluated visually (erythema) and by palpation (infiltration) with scores ranging from 0 (absent) to 3 (severe). The procedure is repeated daily until the 10/11 day; clearing of psoriasis is observed.

15 Example 23

[0092] A topical suspension composition is prepared containing the following ingredients (in parts by weight) as an oil-in-water emulsion gel:

20	Compound B	0.3
	Paraffin, thick	15
	glycerol monostearate	0.3
	propylene glycol	10
25	Carbopol 974p	0.5
	Carbopol 1342	0.5
	NaOH 5%	2.5
	sorbic acid	0.1
30	water	70.8

[0093] The composition is prepared by mixing together the compound and other ingredients. The composition is subjected to stress conditions in a centrifuge for 24 hours at a temperature of up to 95°C. No degradation of the active agent is observed using HPLC.

35 **[0094]** Suspension compositions are prepared in Examples 24 to 30.

Example 24	Amount (g/100g)
Compound B	0.1
Paraffin, thick	48
Glycerol monostearate	8
Petrolatum, white	43.9

Example 25	Amount (g/100g)
Compound B	0.1
Paraffin, thin	20
Petrolatum, white	71.9
Wax, microcrystalline	8

Example 26	Amount (g/100g)
Paraffin, thick	30
Cetyl alcohol	5
Stearyl alcohol	5
Sorbitan monostearate	2

EP 1 147 766 B1

(continued)

Example 26	Amount (g/100g)
Polysorbate 80 (polyhydroxyethylensorbitanmonooleate)	4
Glycerol monostearate	3
Ascorbyl palmitate	0.05
Compound B	0.1
Sorbic acid	0.1
Propylene glycol	5
Water	45.75

Example 27	Amount (g/100g)
Propylene glycol	10
Paraffin, thick	15
Compound B	0.1
Carbopol 1342 (Polyacrylic acid, partly long chain alkylester)	1
Methyl Parabens	0.07
Propyl Parabens	0.03
NaOH aqueous solution 5%	2.5
Water	71.30

Example 28	Amount (g/100g)
Compound B	0.1
Carbopol 947	1
NaOH aqueous solution IN	2.5
Water	96.4

Example 29	Amount (g/100g)
Compound B	0.1
Cetylstearyl alcohol	0.5
Wool wax alcohols	6
Petrolatum, white	93.4

Example 30	Amount (g/100g)
Compound B	0.1
Cetylstearyl alcohol	0.25
Wool wax alcohols	3
Petrolatum, white	46.65
Water	50

[0095] Good to very good stability is observed for the suspension compositions of Examples 24 to 30. The suspensions are applied to healthy volunteers and are found to be well tolerated. Compound B may be replaced by compound 1, 2, 3, A, C or D in any of the compositions as described in Examples 23 to 30.

Claims

1. A topical composition in the form of an emulsion that comprises a compound of the FK506 class; a physiologically

EP 1 147 766 B1

acceptable alkanediol, ether diol or diether alcohol containing up to 8 carbon atoms as solvent for the compound of the FK506 class; and water; **characterised in that** it further comprises an unsaturated fatty alcohol.

- 5
2. A topical composition according to claim 1 wherein the compound of the FK506 class is ascomycin, 33-epi-chloro-33-desoxyascomycin or FK506.
3. A topical composition according to claim 1 wherein the compound of the FK506 class is 3 3-epi-chloro-3 3-desoxyascomycin.
- 10
4. A topical composition according to any preceding claim in which the solvent is hexylene glycol or propylene glycol.
5. A topical composition according to any preceding claim in which the unsaturated fatty alcohol is oleyl alcohol.
- 15
6. A topical composition according to claim 1 which is in the form of an oil-in-water emulsion gel comprising
- a) a macrolide which is a compound of the FK506 class in an amount of up to 5 weight %;
- b) a polymeric thickener for the continuous aqueous phase in an amount of up to 20 weight %;
- c) a hydrophilic component as solvent which is propylene glycol in an amount of up to 40 weight %;
- 20
- d) one or more organic acids in a total amount of up to 5 weight %;
- e) one or more stabilisers which are unsaturated fatty alcohols in a total amount of up to 5 weight %; and
- f) water in an amount of up to 90 % by weight.

Patentansprüche

- 25
1. Topische Zusammensetzung in Form einer Emulsion, die eine Verbindung der FK506 Klasse; ein physiologisch annehmbares Alkandiol, Etherdiol oder einen Dietheralkohol mit bis zu 8 Kohlenstoffatomen als Lösemittel für die Verbindung der FK506 Klasse und Wasser umfasst; **dadurch gekennzeichnet, dass** sie zusätzlich einen ungesättigten Fettalkohol umfasst.
- 30
2. Topische Zusammensetzung nach Anspruch 1, wobei die Verbindung der FK506 Klasse ein Ascomycin, 33-Epichlor-33-desoxyascomycin oder FK506 ist.
3. Topische Zusammensetzung nach Anspruch 1, wobei die Verbindung der FK506 Klasse 33-Epichlor-33-desoxyascomycin ist.
- 35
4. Topische Zusammensetzung nach einem beliebigen vorstehenden Anspruch, in der das Lösemittel Hexylenglykol oder Propylenglykol ist.
- 40
5. Topische Zusammensetzung nach einem beliebigen vorstehenden Anspruch, in welcher der ungesättigte Fettalkohol Oleylalkohol ist.
6. Topische Zusammensetzung nach Anspruch 1, die in Form eines Öl-in-Wasser Emulsionsgels vorliegt, umfassend:
- 45
- a) ein Makrolid, das eine Verbindung der FK506 Klasse ist, in einer Menge von bis zu 5 Gew.-%;
- b) ein polymeres Verdickungsmittel für die kontinuierliche wässrige Phase in einer Menge von bis 20 Gew.-%;
- c) eine hydrophile Komponente als Lösemittel, das Propylenglykol ist, in einer Menge von bis zu 40 Gew.-%;
- d) eine oder mehrere organische Säuren in einer Gesamtmenge von bis zu 5 Gew.-%;
- 50
- e) einen oder mehrere Stabilisatoren, die ungesättigte Fettalkohole sind, in einer Gesamtmenge von bis zu 5 Gew.-%; und
- f) Wasser in einer Menge von bis 90 Gew.-%.

Revendications

- 55
1. Composition topique sous forme d'une émulsion, qui comprend un composé de la classe du FK506 ; un alcanediol, étherdiol ou diéther-alcool physiologiquement acceptable contenant jusqu'à 8 atomes de carbone comme solvant pour le composé de la classe du FK506 ; et de l'eau, **caractérisée en ce qu'elle** comprend en outre un alcool

EP 1 147 766 B1

gras insaturé.

- 5
2. Composition topique selon la revendication 1, dans laquelle le composé de la classe du FK506 est l'ascomycine, la 33-épi-chloro-33-désoxyascomycine ou le FK506.
- 10
3. Composition topique selon la revendication 1, dans laquelle le composé de la classe du FK506 est la 33-épi-chloro-33-désoxyascomycine.
4. Composition topique selon l'une quelconque des revendications précédentes, dans laquelle le solvant est l'hexylène-glycol ou le propylène-glycol.
- 15
5. Composition topique selon l'une quelconque des revendications précédentes, dans laquelle l'alcool gras insaturé est l'alcool oléylique.
6. Composition topique selon la revendication 1, qui se présente sous forme d'un gel en émulsion huile-dans-eau, comprenant :
- 20
- a) un macrolide qui est un composé de la classe du FK506 en une quantité pouvant atteindre 5 % en poids ;
- b) un épaississant polymère pour la phase aqueuse continue en une quantité pouvant atteindre 20 % en poids ;
- 25
- c) un constituant hydrophile, à titre de solvant, qui est le propylène-glycol, en une quantité pouvant atteindre 40 % en poids ;
- d) un ou plusieurs acides organiques en une quantité totale pouvant atteindre 5 % en poids ;
- e) un ou plusieurs stabilisants qui sont des alcools gras insaturés en une quantité totale pouvant atteindre 5 % en poids ; et
- 30
- f) de l'eau, en une quantité pouvant atteindre 90 % en poids.
- 35
- 40
- 45
- 50
- 55